Reactivity of Intrarenal Arteries to Vasoconstrictor and Vasorelaxant Polypeptides in Adult Stroke-Prone Spontaneously Hypertensive Rats

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Abstract

The reactivity of intrarenal arteries to vasoconstrictor and vasodilator polypeptides was examined in adult stroke-prone spontaneously hypertensive rats (SHRSP). The contraction response to endothelin-1 (ET-1) was greater in SHRSP than in age-matched Wistar-Kyoto rats (WKY), and so was the pD_2 estimate (8.05 ± 0.03 in SHRSP, and 7.73 ± 0.06 in WKY; $n=5$, $P<0.05$). The contraction response to, and the pD_2 estimate of, vasopressin were comparable in SHRSP and WKY. Neuropeptide Y did not contract the intrarenal arteries. In norepinephrine-precontracted arteries with intact endothelium, substance P and neurokinin A did not relax the arteries of either SHRSP or WKY, while calcitonin gene-related peptide (CGRP) induced a profound relaxation response. Relaxation response to CGRP was significantly greater in SHRSP than in WKY. Atrial, brain, and C-type natriuretic peptides (ANP, BNP, CNP), vasoactive intestinal polypeptide (VIP), and peptide histidine isoleucine (PHI) all caused relaxation responses, with a greater extent of relaxation to ANP, BNP, and VIP and a less extent to CNP and PHI. However, there were no significant differences in these relaxation responses between SHRSP and WKY. The current results revealed the character of heterogeneity of rat intrarenal arteries in response to vasoconstrictor and vasodilator peptides, and showed an enhanced reactivity to ET-1 and to CGRP in SHRSP.

Key words: calcitonin gene-related peptide (CGRP), endothelin, renal artery, SHRSP.

Introduction

Although spontaneously hypertensive rats (SHR) have been widely used in the study of essential hypertension for decades, the exact mechanisms underlying the development and maintenance of SHR high blood pressure have not yet been fully characterized. Renal cross

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transplantation experiments have shown that genetically normotensive recipient rats develop hypertension after transplantation of kidneys from genetically hypertensive donor rats (even from donor rats at prehypertensive stage or those continuously treated with antihypertensive agents) (De Wardener, 1990 ; Rettig *et al.*, 1990, 1993). Furthermore, a recent study has shown that genetically hypertensive recipient rats lowered their blood pressure after kidney transplantation from normotensive donors (Patschan *et al.*, 1997). This increasing evidence suggests that the kidney abnormality is likely to be a causative factor for SHR hypertension.

It has been reported that renal vascular resistance in SHR is enhanced (Arendshorst and Beierwaltes, 1979). Since renal vascular beds play an important part in maintaining total peripheral resistance, and act as one of the main contributors to blood pressure formation, an increase of renal vascular resistance will directly contribute to blood pressure elevation. Increase of renal vascular resistance may also result in sodium retention by reducing renal blood flow, which may further accelerate hypertension genesis indirectly.

A body of evidence has suggested that some vasoactive polypeptides like calcitonin gene-related peptide (CGRP), atrial natriuretic peptide (ANP), vasoactive intestinal polypeptide (VIP), may be involved in the hypertensive process of SHR or stroke-prone SHR (SHRSP) (Scott and Pang, 1983 ; Lee *et al.*, 1988 ; Kawasaki *et al.*, 1990). We previously found that the relaxant response to CGRP was significantly exaggerated in the intrarenal arteries (IRA) of SHRSP and SHR (Gao *et al.*, 1994), indicating that the peptidergic regulation of IRA function is altered in these hypertensive rats. The reactivity of the IRA of these hypertensive rats to vasoconstrictor and to other vasorelaxant peptides, however, has not been addressed. In this study, therefore, to characterize other possible alteration(s) in reactivity to vasoactive peptides in the IRA of SHRSP we examined the response to vasoconstrictor peptides, and to vasodilator peptides in comparison with that to CGRP.

Materials and Methods

Animals

The study was performed on male SHRSP and WKY at the age of 24-28 weeks. The rats were bred and maintained at the Experimental Animal Center of Kinki University School of Medicine. The systolic blood pressure was 241.9 ± 4.3 ($n=32$) and 148.6 ± 5.7 ($n=28$) mmHg for SHRSP and WKY, respectively (tail cuff method).

Experimental Protocols

The protocol was approved by Animal Care Committee of Kinki University School of Medicine. The methods have been described in detail in our previous paper (Gao *et al.*, 1994). Briefly, the ring segments (approximately 1 mm long) of the third order branch of renal artery were horizontally mounted on two L-shaped tungsten wires (50 μ m in diameter) with 200 mg resting tension in a chamber (2 ml) filled with Krebs-Henseleit solution. The solution was constantly bubbled with mixed gas of 95% O₂ and 5% CO₂ and maintained at 37°C. Changes of tension were isometrically recorded. The viability of the artery preparation was tested with KCl (40 mM), and the integrity of endothelium was functionally assessed with acetylcholine

(10^{-6} M) in a norepinephrine-precontracted state. The artery was abandoned if the relaxation to acetylcholine was less than 30% of papaverine-induced maximal relaxation. The concentration-response curve of vasoconstrictor peptides was assessed in quiescent state, and the response to vasorelaxant peptides was established in norepinephrine (NE, $6-8 \times 10^{-7}$ M)-precontracted rings. The precontraction to NE was stable and well maintained during the experiment.

Chemicals

All the peptides used in this experiment were the products of Peptide Institute Inc. Japan. Acetylcholine chloride was from Daiichi, Japan; Norepinephrine bitartrate was from Sigma, USA; Papaverine hydrochloride was from Dainippon, Japan. All concentrations given were final concentrations in the bath chamber.

Statistics

The contraction response to peptides was normalized by the contraction to 40 mM KCl. The magnitude of 40 mM KCl-induced contraction was comparable in SHRSP and WKY (SHRSP: 176.3 ± 28.4 , WKY: 172.5 ± 32.8 , $n=6-8$, in mg). The relaxation response to peptides was normalized by the maximal relaxation response generated by 10^{-4} M papaverine. Results were expressed as mean $\pm$ s.e.m. for n separate experiments. The pD_2 estimate was determined by regression analysis as $-\log$ concentration that produced 50% of that agonist's maximal response observed. Significance was determined by Student's unpaired t -test. $P < 0.05$ was considered as statistically significant.

Results

Contraction Response to endothelin-1 (ET-1), Arg⁸-vasopressin and neuropeptide Y

ET-1 produced a profound contraction response of the IRA in a concentration-related manner at the range of 3×10^{-9} to 10^{-7} M. A greater percentage of contraction was observed in SHRSP when compared to that of WKY at all the concentrations except the lowest and the highest (Fig. 1A). The pD_2 estimate of ET-1 was higher in SHRSP than in WKY (8.05 ± 0.02 in SHRSP, 7.73 ± 0.06 in WKY; $n=4-5$, $P < 0.01$). Vasopressin also potently contracted the artery, but the magnitude of contraction to all of the concentrations and the pD_2 estimates were comparable in SHRSP and in WKY (pD_2 estimates: 8.56 ± 0.09 in SHRSP ($n=5$), and 8.53 ± 0.07 in WKY ($n=6$)) (Fig. 1B). As shown in Fig. 1C, neuropeptide Y caused neither any observable contraction, nor relaxation of the IRA at resting or precontracted state at all of the concentrations ranging from 10^{-8} M to 10^{-6} M.

Effects of Substance P and Neurokinin A, in comparison with CGRP

In NE-precontracted arteries, neither substance P nor neurokinin A produced any observable relaxation response in SHRSP and WKY (Fig. 2A and 2B). CGRP, at the range of 10^{-11} M to 10^{-7} M, elicited a dose-related relaxation response, and a greater magnitude of relaxation was found in SHRSP when compared to WKY at all concentrations except the lowest (Fig. 2C).

Fig. 1. Contractile effects of endothelin-1 (ET-1) (A), vasopressin (B), and neuropeptide Y (C) on the intrarenal arteries of SHRSP (Δ) and WKY ($\circ$). The contraction was normalized by 40 mM KCl-induced tension. * $P < 0.05$, ** $P < 0.01$ vs WKY ($n = 5-6$, unpaired student's t -test).

Fig. 2. Relaxant effects of substance P (SP) (A), neurokinin A (NKA) (B), and calcitonin gene-related peptide (CGRP) (C) on the intrarenal arteries of SHRSP (Δ) and WKY ($\circ$). Arteries were pre-contracted with norepinephrine. Relaxation was expressed as % of the maximal relaxation response to papaverine (10^{-4} M). ** $P < 0.01$ vs WKY ($n = 5-6$, unpaired Student's t -test).

The pD_2 estimate of CGRP was higher in SHRSP (8.85 ± 0.08 , $n = 5$) than in WKY (8.13 ± 0.07 , $n = 6$) ($P < 0.01$).

Fig. 3. Relaxant effects of atrial natriuretic peptide (ANP) (A), brain natriuretic peptide (BNP) (B), and C-type natriuretic peptide (CNP) (C) on the intrarenal arteries of SHRSP (Δ) and WKY ($\circ$). Arteries were pre-contracted with norepinephrine. Relaxation was expressed as % of the maximal relaxation response to papaverine (10^{-4} M). ($n=5-6$, unpaired Student's t -test).

Relaxation Response to ANP, Brain and C-type Natriuretic Peptides (BNP and CNP)

As illustrated in Fig. 3, ANP, BNP and CNP all induced a relaxation response of the IRA. The magnitudes of the maximal relaxation response to ANP and BNP were around 1.5 times greater than that to CNP. The pD_2 estimates of ANP and BNP in SHRSP and WKY (ANP: 8.68 ± 0.07 and 8.63 ± 0.16 ; BNP: 8.87 ± 0.13 and 8.94 ± 0.17) were significantly higher than that of CNP (7.69 ± 0.04 and 7.6 ± 0.06) ($P < 0.01$, $n=4-5$). However, there were no significant

Fig. 4. Relaxant effects of vasoactive intestinal peptide (VIP) (A) and peptide histidine isoleucine (PHI) (B) on the intrarenal arteries of SHRSP (Δ) and WKY ($\circ$). Arteries were contracted with norepinephrine. Relaxation was expressed as % of the maximal relaxation response to papaverine (10^{-4} M). ($n=5-6$, unpaired Student's t -test).

differences in either the relaxation responses or the pD_2 estimates of these peptides between SHRSP and WKY.

Relaxant Response to VIP and Peptide Histidine Isoleucine (PHI)

VIP (10^{-11} M to 10^{-7} M) and PHI (10^{-9} M to 10^{-7} M) generated a concentration-dependent relaxation response in the IRA of SHRSP and WKY. The magnitude of maximal relaxation response to VIP was about 3 times greater than that to PHI, as shown in Fig. 4. The pD_2 estimates of VIP (SHRSP: 8.29 ± 0.09 , WKY: 8.3 ± 0.14) were also greater than that of PHI (SHRSP: 7.71 ± 0.06 , WKY: 7.68 ± 0.1) ($P < 0.05$, $n = 5$). However, there were no differences between SHRSP and WKY in reactivity to either VIP or PHI.

Discussion

In this study we examined the reactivity of IRA of SHRSP to vasoconstrictor and vasodilator peptides. Rat IRA exhibited heterogeneous reactivity to vasoactive peptides: higher reactivity to constrictor peptides ET-1 and vasopressin and to vasorelaxant peptides CGRP, ANP, BNP and VIP; lower reactivity to vasorelaxant peptides CNP and PHI. Substance P, neurokinin A, and neuropeptide Y did not cause observable responses. In the IRA of SHRSP, the reactivity to ET-1 and to CGRP was greatly enhanced.

Many studies have shown that endothelins are potent renal vasoconstrictors that enhance renovascular resistance (King *et al.*, 1989; Loutzenhiser *et al.*, 1990; Fretschner *et al.*, 1991). In the main trunk of the renal artery or on a perfused kidney of SHR, a higher sensitivity of the renal vasculature to endothelins has been reported (Tomobe *et al.*, 1988; Miyauchi *et al.*, 1989; Evangelista *et al.*, 1992). In this study, we provided direct functional evidence showing the hypersensitivity of IRA to ET-1. Receptor autoradiography and molecular biological studies have revealed an overexpression of ET receptors in the intrarenal branches of the renal artery (Hochoer *et al.*, 1996) and an altered ratio of ET receptor subtypes in the cortex of SHR kidneys (Gellai *et al.*, 1994). Furthermore, there has been a report showing that the content of immunoreactive ET-1 is much lower in the kidney of SHR than in WKY (Kitamura *et al.*, 1989). Based on these observations, we postulate that the hypersensitivity to ET-1 shown in the IRA of SHRSP is likely to be the consequence of upregulation of ET receptors, and this upregulation may act to compensate for the lower concentration of ET in the SHRSP kidney. The pathophysiological significance of the increased reactivity to ET-1 in the IRA of SHRSP remains obscure. Two distinct subtypes of ET receptors, ET_A and ET_B, have been cloned in mammals (Bax and Saxena, 1994). The current results can not distinguish which subtype is responsible for the enhanced response shown in SHRSP, and further study is needed.

Vasopressin is a strong vessel pressor peptide in renal circulation. It exerts its vasoconstrictor action via specific membrane receptors (Larivière *et al.*, 1989). There is controversy of the effects of vasopressin in SHR: some reports show exaggerated reactivity to vasopressin in perfused SHR or SHRSP kidneys (Berecek *et al.*, 1980; Feng and Arendshorst, 1996), while some others do not (Fink and Brody, 1979; Collis *et al.*, 1980). Our study with isolated IRA of SHRSP showed that the reactivity to vasopressin did not alter in comparison with normoten-

sive WKY, suggesting the renal artery, at least the intrarenal segment we used, did not have hyperactivity to vasopressin. Neuropeptide Y, which itself is a potent vasoconstrictor in rats (Zukowska-Grojec *et al.*, 1987; Andriantsitohaina and Stoclet, 1988; McAuley and Westfall, 1992), is usually co-localized with norepinephrine in perivascular sympathetic nerves (Ekblad *et al.*, 1984). A number of reports have shown hyperactivity of peripheral sympathetic nerves including the renal nerve in SHR (Okamoto *et al.*, 1967; Coote and Sato, 1977; Thoren, 1987). However, the IRA of SHRSP and WKY did not react to exogenously applied neuropeptide Y. Our results indicate that neuropeptide Y is not an effective regulator of IRA function.

As we have demonstrated previously (Gao *et al.*, 1994), the IRA of SHRSP exhibited higher reactivity to CGRP, and we hypothesized this hyperactivity to CGRP to be the consequence of upregulation of CGRP receptors due to dysfunction of CGRP-containing perivascular nerves. An increase of reactivity to CGRP may compensate, at least partially, for the decreased function of CGRP-containing prevascular nerve and may help to decrease high blood pressure by improving vasodilation, if there is sufficient CGRP available. In this study, we examined the reactivity to substance P and to neurokinin A, the two most abundant peptides which may co-localize with CGRP in sensory nerve fibers (Holzer, 1988). However, neither substance P nor neurokinin A produced any observable response up to the concentration of 10^{-6} M, a 10 fold higher concentration than that of CGRP at which the maximal relaxation response was induced. Our functional results suggested that rat IRA lacked receptors of these tachykinins and were in agreement with previous immunohistochemical findings (Mulder *et al.*, 1985).

Two subtypes of natriuretic peptide receptor (NPR-A and NPR-B) have been proposed (Kollen *et al.*, 1991). The NPR-A receptor is relatively more sensitive to ANP and BNP, while NPR-B receptor is relatively more responsive to CNP (Suga *et al.*, 1992). Receptor autography study also revealed that ANP and BNP shared binding sites in rat kidney (Oehlenschläger *et al.*, 1989). Among the natriuretic peptide family, ANP and BNP potently dilated rat IRA, whereas CNP displayed a much weaker action. This implies that the main subtype of natriuretic peptide receptor in rat IRA is NPR-A. The reactivity of IRA of SHRSP to these natriuretic peptide family members did not differ from that of WKY, suggesting their role in regulating IRA function is not altered. In contrast, the report by Wei *et al.* (1994) showed an increased relaxation response to ANP and a reduced relaxation response to CNP in the aorta of SHR. The differences between our results and theirs may be due to the difference in arteries employed, the IRA vs aorta, or to the difference in rats used, SHRSP vs SHR.

In the mesenteric arteries of SHRSP, an increased density of VIP-containing innervation has been reported (Lee *et al.*, 1988). We found, in this experiment, that VIP induced a moderate relaxation response, and that PHI, a homologous peptide of VIP (Lundberg *et al.*, 1984), caused a slight relaxation response in the IRA, but there were no significant differences between SHRSP and WKY. These results indicated that the reactivity to VIP and to PHI were not changed in the IRA of SHRSP.

Throughout this study, we found that rat IRA was highly sensitive to ET-1, vasopressin, CGRP, ANP, BNP and VIP, less sensitive to CNP and PHI, and did not react to neuropeptide Y, substance P and neurokinin A. These differences in reactivity suggest different roles of these peptides in modulating the IRA function. In SHRSP, ET-1 induced contraction and

CGRP-induced relaxation were significantly increased, indicating these two peptides are possibly involved in the pathophysiological process of hypertension.

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